REMARKS

Claims 38-74 are pending in the application.

The Rejection Under 35 U.S.C. § 112 Is In Error

Claims 38-74 are rejected under 35 U.S.C. 112, first paragraph, for a lack of enablement for a method of treating colorectal cancer, a method of treating pre-malignant colorectal adenoma, or a method or preventing colorectal cancer in a human. Applicants respectfully disagree.

In particular, the Examiner has rejected the claims under the basis (i) that the specification does not show the data from which Applicant has concluded that black tea extract has an effect on cox-2 gene expression (page 5, lines 2-6, of the Office Action), and (ii) that the result of the administration of the extract is unpredictable in the absence of appropriate experimental evidence (page 5, lines 13-17).

According to the Examiner, Applicants disclose assays for DNA fragmentation analysis, Northern blot analysis, reverse transcription polymerase chain reaction, and Western blot analysis in the application but do not show the data from which Applicants have concluded that the claim-designated extract has an effect on modulating cox-2 gene expression.

In response, Applicants respectfully point out that data demonstrating the enablement of the claimed invention is indeed, present in the application as it was originally filed. See for example, on page 3, line 33 to page 4, line 2; page 4, lines 10-13, lines 24-27, and lines 30-32; page 5, lines 22-24; page 6, lines 1-5, lines 20-25, and lines 31-32. In addition, Applicants invite the Examiner's attention to the Rule 132 Declaration, particularly paragraphs 6.2-6.3, and Exhibit 2, wherein are described in greater detail and in graphical form, the data corresponding to the results disclosed in the application.

The Examiner indicates that even given the in vitro results disclosed in the application, Applicants have not demonstrated a method for treating and/or preventing each of the claim-designated colorectal cancer disease conditions in a human. On page 5, lines 13-17, the Examiner stated that no one skilled in the art would accept that the administration of the claimed composition could function as contemplated in the specification. On page 6, lines 2-9, the Examiner also stated that because there is insufficient guidance in the application as to how to carry out the claimed method of cancer treatment, a lack of correlative working examples, the claims would require an undue amount of experimentation without a predictive degree of success on the part of the skilled artisan.

Applicant points out that the Examiner's arguments on a lack of predictability essentially amount to an allegation of lack of utility. The Utility Guidelines (MPEP 2107 and 2164.07) are applicable when there is an allegation of lack of utility under § 112. Under the Utility Guidelines, evidence of utility is sufficient if it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. If reasonably correlated to a particular pharmaceutical utility, data generated using in vitro assays, or from testing in an animal model, or a combination of both, almost invariably will be sufficient to establish the asserted utility. Lack of an appropriate animal model to assess effectiveness of a treatment modality prior to the filing date should not itself preclude a finding that an invention has utility. There is no requirement to provide data from human clinical trials for establishing utility of an invention related to treatment of human disease. All that is required is a reasonable correlation between the effectiveness of the methods and the asserted use. Applicant respectfully emphasizes that the evidentiary standard applicable to prove enablement is similar to that for proving utility, which is a reasonable correlation between the Applicant's data and the asserted efficacy of the claimed invention. Here, the results showing that black tea extract reduced human colon cancer cell numbers and modified human colon cancer cell morphology reasonably correlates with its application in humans.

In section 6 of the Rule 132 Declaration, one of the inventors, Dr. Ho, discusses the experimental data obtained from cell cultures which were presented in the application as filed (see pages 3 to 6 of the specification) and concludes that one of skill in the art would appreciate that the methods as claimed would work successfully.

In section 7 and Exhibit 3 of the Rule 132 Declaration, Dr. Ho describes experimental results obtained in vivo which provide further evidence of utility and enablement of the instant invention. In particular, Min mice, which are art-accepted models of colorectal cancer, that develop intestinal cancer spontaneously due to a gene mutation, were orally administered black tea extract comprising theaflavin 3-gallate and theaflavin-3' gallate as disclosed in the application (see page 7, lines 32-34). The results indicate a lower incidence of colon tumors as well as a low number of colon tumors per mouse. In addition, Min mice given the black tea extract also exhibited lower incidence of small and large intestinal tumors. Dr. Ho concludes in paragraph 7.7 that he and one skilled in the art would conclude, in view of the data presented in Exhibit 3, that theaflavin 3-gallate and theaflavin-3'gallate have utility for the treatment and prevention of colon cancer.

In view of the evidence provided in Exhibit 3, it is also apparent that no undue experimentation is required to make black tea extract and use the extract against colon cancer given the guidance provided in the present application and knowledge in the art. Applicants further submit that the skill in the respective fields of molecular biology and cancer medicine is high, and that general methods for assaying medical benefits and determining dosage, are well known. Where a disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and where, at the time of application, the skill in the art was quite high and the methods needed to practice the invention well known, a conclusion of enablement should be made. In re Wands, 858 F.2d 731, 740, 8 U.S.P.Q.2d. 1400, 1406 (Fed. Cir. 1988).

The Examiner's attention is also directed to the opinion of the Court of Appeals for the Federal Circuit (C.A.F.C.) in In re Brana, 5 F.3d 1557, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In In re Brana, the C.A.F.C. reversed the Board's decision and explained the legal standard for compliance with the relevant § 112 requirement that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support," a specification's disclosure "must be taken as in compliance with the enabling requirement." Id. at 1441 (emphasis in the original).

In In re Brana, mice were injected with specific leukemias for use as test subjects to measure the antitumor properties of the claimed compounds. This is analogous to the experiments described in Exhibit 3, wherein mice that are prone to develop intestinal cancer were given black tea extract to demonstrate the effect of theaflavin 3-gallate and theaflavin-3' gallate on colon carcinogenesis in vivo. According to In re Brana at 1437, test results showing antitumor activity of compounds against a standard tumor model in vivo is acceptable as evidence of utility sufficient to meet the requirement of 35 U.S.C. § 112, first paragraph.

Applicants respectfully point out that, other than alleging insufficient evidence in the specification or general unpredictability of the claimed methods, the Examiner has not come forward with any particular evidence as to why black tea extract would necessarily act differently in the human body than to human colon cancer cells. The Examiner only referred to Jain (Science, 1996. Vol. 271:1079-1080) and Dermer (Bio/Technology, 1994. Vol. 12: 320) in support of the contention (page 5 of the Office Action, paragraph starting on line 7). However, the necessary burden that the Patent and Trademark Office bears in establishing a *prima facie* case of non-enablement has not been met. A specification and claims of corresponding scope must be taken as *prima facie* in compliance with § 112 unless specific and articulated reasons to the contrary are offered. The Examiners' contention and argument in support of the instant rejection are circumstantial and conclusory.

For example, the Examiner alleges that Dermer teaches that cell lines provide a poor model for human cancer because cell lines often lack the pathways required for real cancer *in vivo*. Applicants respectfully point out that, contrary to the Examiner's allegation, cell lines are widely recognized as models for human cancer by one of skill in the art. See, *e.g.*, Sacks, 1996, Cancer and Metastasis Reviews 15:27-51 (hereinafter "Sacks"), and Drexler, 1995, Leukemia Research 19:681-691 (hereinafter "Drexler"), copies of which are supplied respectively, as references C12 and C15 in the accompanying Supplemental Information Disclosure Statement.

Briefly, Sacks discloses the use of several hundred head and neck squamous cell carcinoma cell lines for studying a broad spectrum of head and neck cancer (see, *e.g.*, abstract on page 27 and summary on page 40 to 41 of Sacks). Drexler discloses the use of leukemia cell lines as *in vitro* models for studying leukemia (see, *e.g.*, abstract on page 681). Drexler also states in the last sentence of the second column on page 689 that "[i]mmortalized hematopoietic cell lines continue to be valuable, if not indispensable tools in basic and clinically-oriented leukemia research." Thus, Applicants submit that these examples illustrate that one of skill in the art at the time the application was filed would have recognized cancer cell lines as *in vitro* models of human cancer.

Moreover, in the present case as discussed in detail above, Applicants submit that the in vivo data presented in the Rule 132 Declaration shows that the data obtained from cancer cell lines really was indicative of what would happen in an animal.

In view of the foregoing, Applicants submit that the rejection is erroneous and requests its withdrawal.

CONCLUSION

In light of the above remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: June 30, 2006

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